REMARKS/ARGUMENTS

At the outset, Applicants representative Paul Fehlner and the undersigned would like to thank Examiner Pak for the courtesies extended during the telephonic interview on January 27, 2005. During the interview, the rejections under the written description and enablement requirements were discussed. The Examiner clarified that she had intended the enablement rejection to also encompass claims 18-20. Accordingly, Applicants will also address the enablement rejection with respect to claims 18-20. In addition, proposed claim amendments, which are set forth in the instant amendment, were discussed with the Examiner. The Examiner acknowledged that the arguments and amendments set forth during the interview would, at a minimum, possibly result in withdrawal of the enablement requirement. Lastly, Applicants' representatives requested that the Examiner acknowledge the response to the 102(g) rejection in the previously filed response. The Examiner indicated that she would acknowledge this response.

Claims 8, 13, 18, 47, 48, and 49 have been amended. Claims 1-7, 16 and 30-36 have been cancelled, without prejudice or disclaimer. Claims 56-68 have been added. Claims 8-15, 17-29, 37-41 and 45-68 (of which claims 21-29, 37-41, 45 and 46 have been withdrawn from consideration; and of which claims 11, 12 and 54 have only been objected to for depending from a rejected base claim, but would be allowable if rewritten into independent form) are pending in this application upon entry of this amendment.

Claims 8, 13, 47, 48, and 49 have been amended to recite that the claimed nucleic acid "comprises four copies of a scavenger receptor cysteine rich domain having a sequence at least

about 80% identical to a sequence selected from the group consisting of SEQ ID NOs: 3, 4, 5, and 6." Support for this amendment can be found throughout the specification, and in particular on page 9, lines 4-8; page 18, line 28 - page 19, line 4; page 7 lines 3-7, and original claims 1 and 13.

Claim 18 has been amended to recite that the oligonucleotide hybridizes with a nucleotide that has the sequence depicted in SEQ ID NO: 1 under stringent conditions that correspond to 50% formamide, 4XSSC at 42°C. Support for this amendment is found throughout the specification, and in particular on page 19, line 28 - page 20, line 4.

Support for new claim 56 can be found throughout the specification, and in particular on page 20, lines 5-10.

Support for new claim 57 can be found throughout the specification, and in particular on page 20, lines 5-10.

Support for new claim 58 can be found throughout the specification, and in particular on page 4, line 9; page 22, line 24; page 47, lines 21-23 and original claim 8.

Support for new claim 59 can be found throughout the specification, and in particular on page 4, lines 9-11; page 19, lines 25-27; page 44, line 27 - page 45, line 1 and original claim 10.

Support for new claim 60 can be found throughout the specification, and in particular on page 4, line 9; page 22, line 24; page 47, lines 21-23 and original claim 8.

Support for new claim 61 can be found throughout the specification, and in particular on page 4, lines 9-11; page 19, lines 25-27; page 44, line 27 - page 45, line 1 and original claim 10.

Support for new claim 62 can be found throughout the specification, and in particular on 4, line 9; page 22, line 24; page 47, lines 21-23 and original claim 8.

Support for new claim 63 can be found throughout the specification, and in particular on page 4, lines 9-11; page 19, lines 25-27; page 44, line 27 - page 45, line 1 and original claim 10.

Support for new claim 64 can be found throughout the specification, and in particular on page 8, lines 20-22.

Support for new claim 65 can be found throughout the specification, and in particular on page 19, line 28- page 20, line 4.

Support for new claims 66 and 67 can be found throughout the specification, and in particular on page 4, lines 9-10; Example 2 (page 47, line 25 - page 48, line 29 and in originally filed claim 16.

Support for new claims 68 can be found throughout the specification, and in particular on page 9, lines 9-16 and in originally filed claim 1.

No new matter has been added by way of these claim amendments or new claims.

Rejections under 35 U.S.C. § 112, first paragraph- written description

a. Nucleic acids Encoding EER-7 Proteins

The Examiner has rejected claims 8-10, 13-15, 17, 47-53 and 55 under 35 U.S.C. § 112, first paragraph, contending that the specification lacks an adequate written description to support these claims. These claims are directed to isolated nucleic acids encoding an EER-7 protein which has at least 75-90% sequence similarity to SEQ ID NO: 2, possesses lysyl oxidase

activity, comprises four copies of a scavenger receptor cysteine rich domain having a sequence at least about 80% identical to a sequence selected from the group consisting of SEQ ID NOs: 3, 4, 5, and 6, and comprises a sequence as depicted in SEQ ID NO: 7, *i.e.,* 100% sequence identity to SEQ ID NO: 7. The Examiner contends that claims that recite only 75-90% of the structure of the DNA encoding an EER-7 protein amounts to an insufficient description of the structure of the DNA and that the genus of DNA that would comprise the variants covered by the claims is a large variable genus with the potential to encode many different proteins. The Examiner further argues that the claims cover many structurally related DNAs and that the specification fails to describe any representative species by identifying characteristics or properties other than the "functionality" of encoding an EER-7 protein and fails to provide any structure:function correlation present in all members of the genus. This rejection is respectfully traversed.

While the claims cover a genus, it is not a "large variable genus" as argued by the Examiner. It is certainly not at all clear why a claim to a "large variable genus" is, *per se*, unpatentable because of the written description requirement. The issue is not whether the claimed genus is large or variable, but whether the specification provides an adequate description of the genus in terms such that one of skill in the art would recognize that the inventors possessed the genus. As explained below, the specification not only describes the claimed genus, it describes a broader genus.

The written description requires a writing. See *Enzo Biochem, Inc. v. Gen-Probe Inc.,* 296 F.3d 1316, 1324 (Fed. Cir. 2002); *Regents of University of California v. Eli Lilly & Co.,* 119

F.3d 1559, 1568 (Fed. Cir. 1997). *But* pure words alone, while necessary to an adequate written description, are not in and of themselves sufficient. The words must convey to the skilled artisan what the inventors had invented, and they must enable that invention. The case-law clearly establishes a substantive component to the written description requirement, *Noelle v. Lederman*, 355 F.3d 1343, 1348-49 (Fed. Cir. 2004); *Enzo Biochem,* 296 F.3d at 1324; *Lilly*, 119 F.3d at 1568, though enablement is a distinct requirement from written description. *Enzo Biochem,* 296 F.3d at 1324. The instant specification sets out in clear writing, using terms understandable by the person of skill in the art, the full scope of the generic invention, a novel lysyl oxidase, exemplified by human (and rabbit) orthologs.

It was known by those of skill in the art as early as 1997 that proteins form families with a known set of characteristics. One example of related proteins with a known set of characteristics is orthologs, which refers to genes in different species that apparently evolved from a common ancestral gene by speciation. Normally, orthologs retain the same function through the course of evolution. Identification of orthologs can provide reliable prediction of gene function in newly sequenced genomes. Orthologs often have high sequence similarity. *See Science* (1997) 278:631-7 (attached at Tab 1). Additionally, proteins that are "homologous" possess a common evolutionary origin and include proteins from superfamilies, as well as homologous proteins from different species, *i.e.,* orthologs. These proteins (and their encoding DNA) have a relatively high degree of sequence similarity, whether in terms of percent similarity over the entire length of the protein or the presence of highly conserved residues or motifs. *See*

specification, page 18, lines 7-13. Orthologs and proteins with a common evolutionary origin are examples of the definable genus at issue here.

Given this level of understanding by those of skill in the art, it is clear that the claims themselves constitute an adequate written description. Nevertheless, the specification further explains each of the defining characteristics of the claimed genus. The claims recite both structure and function sufficient to inform the person of skill in the art of their scope. The nucleic acid sequence of the novel species, EER-7, has homology to known lysyl oxidase genes and the previously identified lysyl oxidase catalytic domain is present in the EER-7 protein of the invention. The EER-7 protein also contains four copies of Scavenger Receptor Cysteine Rich ("SRCR") domains, which play a role in protein-protein interactions. *See* specification, page 4, lines 14-19. Sequence comparison studies between human EER-7 and lysyl oxidase ("LO"), lysyl oxidase-like ("LOL"), and WS914 (a novel lysyl oxidase-like protein found in patients with Warner's Syndrome) proteins, as well as EER-7 proteins from other species (*e.g.*, rabbit), demonstrates the description of standard features that characterize the claimed genus, and distinguished it from other genes encoding other lysyl oxidase proteins. Human EER-7 protein is 18% similar in sequence to human LO protein. The catalytic domains of EER-7 and LO protein have a 46% sequence similarity. The catalytic domains of the human LOL and WS914 are 46% and 66% similar in sequence to EER-7, respectively. Three of the four SRCR domains found in EER-7 share about 60% sequence similarity with those in WS914 protein and the fourth shares 34% sequence similarity. *See* specification, page 8, line 27 - page 9, line 8. Furthermore,

EER-7 protein from humans and rabbits share 28% sequence similarity. *See* specification, Figure 1. *See* also specification, page 47, lines 23-24; page 48, lines 15-20; Figures 1 and 2. With regard to function, these proteins are all members of the lysyl oxidase enzymes class of copper amino oxidases, which initiate cross-linking between and within units of elastin and collagen. *See* specification, page 9, lines 9-10. These proteins and their corresponding nucleic acids would be considered "homologous" as it is defined in the specification. They have sequence similarity, conserved motifs, and similar function. They also each have distinct structural features. The human species of EER of the invention has functional and structural features that distinguish it from other lysyl oxidase proteins, such as the control of expression by estrogen and the existence of the four SRCR domains. These sequences and modified characteristics are the ones used by skilled artisans to identify and characterize proteins. Thus, the genus, presently claimed and exemplified by EER-7, is definable and adequately described in the specification using the vocabulary of the art.

In fact, the claims as presently written are narrower in scope than the description of the genus in the specification. The claims require at least 75% overall sequence similarity (similarity to SEQ ID NO: 2) and 100% sequence similarity to the catalytic domain of the LO enzymes (SEQ ID NO: 7). This catalytic domain represents 30% of the sequence of EER-7. As discussed above, the specification adequately describes a genus of related proteins, of which EER-7 is a member, that possess less sequence similarity than what is presently claimed. For example, it exemplifies one in rabbit EER-7. Thus, claims covering proteins with the recited

degree of sequence similarity, structural features and possessing the same function, are clearly supported by the specification.

The Examiner's statement that "many structurally unrelated DNA [sic] are encompassed within the scope of these claims" is unsupported and incorrect. As fully disclosed in the application and discussed above, the claims do not cover structurally unrelated DNAs encoding different proteins. The claims recite a degree of sequence similarity and the presence of identifying domains of the lysyl oxidase family of proteins, as well as the function of such proteins sufficient to inform one of skill in the art what the inventors have invented. The claims, reciting three structural characteristics and one functional characteristic, clearly define a genus of nucleic acid that is fully supported in the specification and entirely consistent with the understanding of this writing by those of skill in the art. The claims would clearly denote to a person of skill in the art that the claimed proteins are part of a recognizable genus of proteins with this structure and function.

Equally incorrect is the Examiner's statement that there is no correlation between structure and function in the claimed genus. As discussed above, this family of proteins, lysyl oxidase enzymes, is defined by their ability to initiate cross-linking between and within units of elastin and collagen. Moreover, every one of the proteins encoded by the nucleic acids in this genus contains the lysyl oxidase catalytic domain set forth in SEQ ID NO: 7. Since every protein in the genus has both the described function and the conserved catalytic domain, there is

indeed a structure/function correlation for the genus, which is adequately described in the specification.

In light of these facts, the Examiner's rejection contradicts the case law from the Court of Appeals for the Federal Circuit. The *Lilly* case supports a finding of written description in this case. The Court in *Lilly* held that an adequate written description of cDNA describing rat insulin did not support generic claims covering cDNA to vertebrate and mammalian insulin.

The Federal Circuit explained:

> In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within the definition. It does not define *any structural features commonly possessed by members of the genus that distinguish it from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of members of the genus.*

Id. at 1568 (*emphasis* added)

The claims at issue do describe the genus by function, *i.e.,* lysyl oxidase activity, but also describe "structural features commonly possessed by members of the genus," *e.g.,* the similarity with the sequence of the EER-7 protein and the SRCR sequences, as well as 100% sequence identity to the conserved catalytic domain of all lysyl oxidase enzymes. The claims at issue fall squarely into the definition of an adequate written description set forth by the Court in the *Lilly*

case; they define structural features commonly possessed by members of the genus that distinguish it from others.[1]

The *Lilly* case also illustrates an important point missed by the Examiner: written description is determined from the viewpoint of a person of skill in the art, not the patent examiner or the courts. *Lilly*, 119 F.3d at 1566. In this case, the EER-7 protein and the DNA encoding it are novel, so a person of skill in the art would not have seen such a protein or DNA before. However, the description in terms of structure and function in both the specification and the claims is sufficient such that a person of skill in the art would clearly recognize that applicants had possession not only of the species, human EER-7 protein and the DNA that encodes the human protein, but the of orthologs in the genus to which EER-7 belongs. Once again, this is because this small definable genus is adequately described by its function as a lysyl oxidase enzyme, its conserved motifs and its sequence identity.

Another decision from the Court of Appeals for the Federal Circuit, *Enzo Biochem*, also shows that the written description adequately supports the claims at issue. In *Enzo*, the Court held that it is not correct that all functional descriptions of genetic material fail to meet the written description requirement. The Court further stated, quoting the Patent Office Guidelines,

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[1] Were the claims to recite "a nucleic acid encoding reptilian EER-7" or "marmoset EER-7," and the specification failed to set forth structural features characteristic of either EER-7, the Examiner might have a point. Similarly, had the patentees in *Lilly* claimed a nucleic acid encoding a protein comprising an α and a β chain joined by a disulfide link, having x% sequence identify to the sequence of rat insulin, and having insulin like activity, the case would have come out differently. While considering such hypothetically is a curious amusement, the real lesson is this: the facts in this case *i.e.*, the language of the claims and the description in the specification, differ from *Lilly* to a degree that precludes arriving at a conclusion of lack of written description. As the Federal Circuit has pointed out, the outcome of these cases turns on the individual facts, not simply a general principal of law, such as 90% identity is never adequately described by the specification. *Enzo Biochem*, 296 F.3d at 1324.

that written description can be met by "show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ... *i.e.,* complete or partial structure, other physical and/or chemical properties, *functional characteristics when coupled with a known or disclosed correlation between function and structure,* or some combination of such characteristics." *Id.* at 1324 quoting *Guidelines for Examination of Patent Applications under 35 U.S.C. § 112, P1 "Written Description" Requirement*, 66 Fed. Reg. 1099, 1106 (emphasis added). As discussed above, the claimed invention is described by a functional characteristic coupled to a disclosed correlation to structure, *e.g.,* lysyl oxidase activity and the conserved catalytic domain, along with two other structural features.

The Examiner has asserted that the specification fails to describe a representative number of species that are required to constitute an adequate written description of a genus. That is a plainly incorrect statement of the law. All that is necessary to support a claim is an adequate description of the structure of the genus in such terms as to distinguish it from other things. *See Enzo Biochem*, 296 F.3d at 1327; *Lilly*, 119 F.3d at 1568. Alternatively, in the *absence* of an explicit description of the features that define the genus, a representative number of species can constitute an adequate description of a genus. ***Id.* at 1569.** As set out in detail above, the specification has a written description of the defining characteristics of the genus. Thus, it is not necessary to have a description of a representative number of species within the genus.

Even applying this erroneous articulation of the written description requirement, the outcome is wrong. The Manual of Patent Examining Procedures states that "[a] 'representative

number of species means that species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus." M.P.E.P. § 2163 at page 2100-174. As discussed above, in this case the genus does not have "substantial variation." Thus, the description of the EER-7 and its relation to the other LO and LOL proteins in the family, is sufficient to support the generic claim, in view of the conserved sequences related to function, as well as the sequence similarity of the members of the claimed genus.

In conclusion, claims 8-10, 13-51, 17, 47-53 and 55 are adequately supported and should be allowed.

b. Oligonucleotides

Claims 18-20, directed to oligonucleotides that are no more than 100 nucleotides in length and comprise at least 20 or 30 consecutive nucleotides of SEQ ID NO: 1 and that hybridize under stringent conditions with a nucleic acid having a nucleotide sequence as depicted in SEQ ID NO: 1, said stringent conditions corresponding to 50% formamide, 4XSSC at 42°C, also stand rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to meet the written description requirement. The Examiner contends that the description of 20-30 consecutive bases out of 3616 nucleotides of SEQ ID NO: 1, which represents less than 1/3 of the whole structure of the nucleotide and less than 1% of the whole structure of the sequence of SEQ ID NO: 1, is insufficient to describe the structure of the oligonucleotides in the claims. The Examiner further argues that because the oligonucleotides can hybridize to any portion of the

sequence, the claims are drawn to a genus of oligonucleotides, with any structure and that the genus is a large variable genus. The Examiner further states that the claims encompass many structurally and functionally unrelated DNAs and that the specification fails to describe any other representative species by identifying characteristics or properties other than comprising 20-30 nucleotides and hybridizing to any portions of SEQ ID NO: 1 and fails to provide any structure:function correlation present in all members of the claimed genus. This rejection is respectfully traversed.

At the outset, Applicants take issue with the logic of the rejection since it creates a requirement for patent claims that find no support in either the statutes or case law. Essentially, the Examiner is rejecting the claims for an inadequate description of limitations that are not recited. There is no argument concerning the description of SEQ ID NO. 1, or 20 to 30 consecutive nucleotides from this sequence. Nor should there be. The claims should face no further scrutiny.

And yet it does. The Examiner, correctly noting that the claims use the term "comprising" argues that the claims do not limit the unrelated features. Where is the requirement in patent law for that? Must a claim for a car comprising a novel tire specify the make and model of the car? Must it even specify that the apparatus comprising the tire is for a car? Must a claim for a composition comprising a novel steroid specify the solvent? In this case it makes no difference what else is present in the oligonucleotide, because if it includes at least 20 consecutive nucleotide bases from SEQ ID NO: 1, a limitation that is supported, enabled,

particular, and distinct, it is within the scope of the claim. The Examiner must provide a legal explanation to conclude otherwise. See *Lilly,* 119 F.3d at 1566 quoting *Lockwood v. American Airlines, Inc.,* 107 F.3d 1565, 1572 (Fed. Cir. 1997) (emphasis added) ("...an applicant complies with the written description requirement 'by describing the invention, *with all of its claimed limitations* ...'")

Claims 18-20 do indeed embrace a genus, a defined one, which is described by a correlated structure and function. The oligonucleotides of the claims *must* comprise 20-30 consecutive nucleotides from SEQ ID NO: 1 (which is double stranded, thus the oligonucleotides may correspond to the sequence from either strand). This structure of the oligonucleotides correlates to their function of being able to hybridize to SEQ ID NO: 1 under clearly defined stringent conditions. Oligonucleotides that comprise at least 20 consecutive nucleotides of SEQ ID NO: 1, can not function properly, *i.e.,* hybridize to SEQ ID NO: 1 under stringent conditions.

Once again the Examiner ignores the requirement that written description be determined by a person of skill in the art. It is well known in the art and set forth in the specification that the appropriate stringency for hybridizing nucleic acids depends on the length and degree of complementation. *See* specification, page 19, lines 16-18. A person of skill in the art would also recognize that oligonucleotides comprising at least 20 consecutive nucleotides of SEQ ID NO: 1 could perform their required function of hybridization. Thus claims 18-20 in light of the specification would compel one of skill to recognize that the applicants had possession of the genus of oligonucleotides that fit the characteristics set forth in the claims.

This rejection is also legally unsound. The Court of Appeals for the Federal Circuit discussed this very type of genus claim in *Enzo Biochem* and stated that the PTO in their Guidelines determined that genus claims to nucleic acids based on their hybridization properties may be adequately described if they hybridize under highly stringent conditions to known sequences because "such conditions dictate that all species within a genus will be structurally similar." *Enzo Biochem.*, 296 F.3d at 1327 quoting *Guidelines,* Example 9, at 35-37. Here the claimed nucleotides must be able to hybridize to a disclosed sequence under conditions described as "highly stringent" in the specification. *See* page 20, lines 1-2 of the specification. Thus, according to both Court and the PTO, these hybridization conditions alone establish the structural similarity between the claimed genus of oligonucleotides, even without the additional requirement that the oligonucleotides comprise at least 20 consecutive base pairs of SEQ ID NO: 1.

Rejections under 35 U.S.C. § 112, first paragraph- enablement

a. Nucleic acids encoding EER-7 Proteins

Claims 8-10, 13-15, 17, 47-53 and 55 also stand rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. The Examiner contends that while the specification enables DNA encoding EER-7 of SEQ ID NO: 2, it does not enable "DNA molecules of unlimited structure." The Office Action argues that the claims drawn to nucleotides that encode EER-7 having "75-90% homology to SEQ ID NO: 2 are broader than the scope enabled by the specification." The Office Action states that the "predictability as to the level of conservation

between the disclosed sequences and those of other EER-7 is extremely complex" and it would not be routine to screen for polynucleotides with a similar sequence. The Examiner also states "[t]he amino acid sequence determines the structural and functional properties of an enzyme. Knowledge of which sequences can be altered or removed and still result in similar protein activity is well outside the realm of routine experimentation." The Office Action concludes that it would require undue experimentation to make DNA encoding EER-7 protein different from SEQ ID NO: 2. This rejection is respectfully traversed.

As an initial matter, the Examiner, in contending that the claims cover "DNA molecules of unlimited structure" concentrates on the claim limitation that the nucleic acid must be at least 75-90% similar in sequence to SEQ ID NO: 2 and ignores the *two additional* recitations of sequence similarity found in the claims. In addition to requiring that the nucleic acid have a high level of overall sequence similarity to SEQ ID NO: 2, *i.e.*, 75-90%,[2] the claims also require 100% sequence similarity to the conserved catalytic domain of LO proteins (which represents 30% of the overall sequence) and 80% identity to four other sequences. When combined, these three structural characteristics do not cover "DNA molecules with unlimited structure," but a clearly defined number of DNA molecules with a highly related structure.

The Examiner also contends that it is outside the realm of routine experimentation to alter the amino acid sequence of a protein and still obtain a protein with similar protein activity. Once

[2] The Examiner states that the claims call for 75-90% homology to SEQ ID NO: 2. This is incorrect. The claims recite 75-90% sequence similarity, which is as quantitative characteristic different than homology. Although homologous sequences will have some degree of sequence similarity, homology relates to a qualitative relationship, *e.g.*, of similar evolutionary origin. *See* specification, page 18, line 20-page 19, line 4.

again, in the case of the claims at issue, this statement is incorrect. While it may the case that a claim reciting DNA with only 75-90% of overall sequence similarity would require undue experimentation to practice, these claims additionally require *100% sequence similarity* to 30% of the overall sequence, which is the functional domain, and four copies of a domain with 80% sequence identity to another sequence. Furthermore, the 100% identity of the catalytic domain directly corresponds to the function of the protein. Thus, this limitation, ignored by the Examiner, provides the additional required guidance needed to make the practice the claimed invention, (*e.g.,* altering the amino acid sequence and obtaining a protein of similar activity), routine to a person of skill in the art.

The Examiner cites *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988) and the factors set forth therein to prove enablement. However, the Examiner does not perform either a full or correct analysis of each factor and thus, has not met the burden of proving non-enablement. When one assesses *all of the limitations* of the claims using the *Wands* factors, it can be seen that these claims are fully enabled.

As discussed above, the specification describes EER-7, a novel LO protein. The specification also fully describes the family of related proteins to which EER-7 belongs, along with their shared function and sequence similarities. The specification contains a full working example of the identification of EER-7 (Example 1, specification, page 44, line 26 to page 47, line 24) as well as the expression of EER-7 and its sequence analysis (Example 2, page 47, line 25 to page 48, line 29). The sequence analysis of the EER-7 protein establishes its structural

similarity with other members of the LO and LOL family, which includes a shared, characteristic catalytic domain associated with LO and LOL proteins, as well as a shared sequence similarity with EER-7 from other species. *See* specification, page 47, lines 21-23; page 48, lines 15-20; Figures 1 and 2. The structural and functional characteristics of the EER-7 protein also distinguish it from the related LOs and LOLs, *e.g.*, the existence of four SRCR domains and the regulation of EER-7 by estrogen. *See* specification, page 4, lines 9-11 and 17-19. Thus, the specification contains working examples that support the making and using of the claimed invention.

The specification contains additional guidance beyond that found in the examples, although well within the skill in the art including more data on the sequence similarity of the members of the protein family (specification, page 4, lines 13-26; page 8, line 27 - page 9, line 8-10), the function of the members of the family (specification, page 9, line 9-10), and methods to obtain and use the nucleic acids of the invention (specification, page 21-29).

The nature of the invention, the state of the art and the predictability of the art are all related in this analysis. The invention includes a novel lysyl oxidase protein and nucleic acids encoding it. The invention can be categorized as one of biotechnology, specifically one using recombinant DNA and mutagenesis techniques. The state of the art in this area is (and was in 2000, the year to which the instant application claims priority) more routine than ever before, as pointed out by the Examiner in the Official Action (page 6), and as shown in the specification by the lengthy list of publications disclosing techniques known and used by those of skill in the art,

all of which date back to the 1980s. *See* specification, page 11, line 25 - page 12, line 6; page 23, lines 9-15. Thus, while biotechnology is often considered to be an unpredictable art, in this case, because of the highly developed state of the art in the particular area of biotechnology being used for the invention, the invention is predictable and routine.

In fact, the Examiner does not seem to rebut this finding and bases the entire argument as to lack of enablement on the large number of DNA molecules that could be covered by the claims. The heart of the rejection can be summarized in the statement "it is not routine in the art to screen a large number of possible combinations." *See* Official Action, page 6 (emphasis in original). In other words, the Examiner believes that a person of skill in the art (whose skill would be quite high) would need to perform an undue amount of experimentation to obtain the nucleic acids of the claims because the number of possible candidates would be unduly large. However, as stated earlier, in making this argument, the Examiner ignores the structural limitations of the claim, including a 100% sequence homology to a conserved region of the protein that is linked to its function. It is uncontroversial in the record that one of skill in the art would be able to determine (1) whether a nucleic acid encodes a protein of the requisite sequence similarity; (2) containing the requisite domains and enzymatic sequence; and (3) having a well-defined enzyme activity. All of these are routine in the art, within the skill of an undergraduate biology major. The Examiner speculates about undefined things that might be, but the specification enables the subject matter of the claim limitations, which are not unduly broad. In other words, the specification enables the subject mater of the claims. Applicants are not aware

of a requirement to enable things that are not within the claims. See *Amgen, Inc. v. Chugai Pharmaceutical Co.,* 927 F.2d 1200, 1213 (Fed. Cir. 1991) ("Moreover, it is not necessary that a patent applicant test all embodiments of his invention, *In re Angstadt,* 537 F.2d 498, 502, 190 USPQ 214, 218 (CCPA 1976); what is necessary is that he provide disclosure to carry out his invention commensurate with the scope of his claims.") See also *Wands*, 858 F.2d at 740 (finding that claims were enabled by an example in the specification "that satisfied all of the claim limitations.")

Also as discussed above, the current claims are narrower in scope than the disclosure supports, *i.e.,* claims to nucleic acids with less sequence similarity than 75%. For example, the specification sets forth the rabbit EER-7 sequence, which is less than 75% similar (see Figure 1).

Therefore, understanding proper analysis of the claim limitations, under the *Wands* factors undue experimentation is not required in making and using the claimed invention. Claims 8-10, 13-15, 17, 47-53 and 55 are fully enabled.

b. Oligonucleotides

Claims 16-18 covering oligonucleotides are also rejected under 35 U.S.C. § 112, first paragraph, as not being enabled. The Examiner contends that an oligonucleotide of 20 base pairs will hybridize to a wide range or polynucleotides and the specification does not teach how to use these varying oligonucleotides. This rejection is respectfully traversed.

Once again, the Examiner has not met the burden of proving non-enablement. The Examiner once again did not consider the claims in light of all of *the recited limitations*, nor did the Examiner do a complete analysis using the *Wands* factors. See *Amgen,* 927 F.2d at 1213; *Wands,* 858 F.2d at 740. Under a correct enablement analysis, claims 16-18 are fully enabled.

The claims are directed to oligonucleotides of no more than 100 nucleotides, with at least 20-30 consecutive nucleotides of SEQ ID NO: 1 that hybridize under stringent conditions to a nucleic acid with the sequence of SEQ ID NO: 1. Stringent conditions are described as corresponding to 50% formamide, 4XSSC, at 42°C.

The claims themselves provide much guidance to a person of skill in the art as to how to make and use the oligonucleotides of the invention, giving not only the length of consecutive base pairs and the sequence to which they should be complementary, but also the hybridization conditions under which the oligonucleotides function. The specification provides even more guidance, setting forth how oligonucleotides can be made (page 20, lines 5-17; page 20, line 28 to page 21, line 22) and discussing hydridization conditions, including those considered "stringent" (specification, page 19, line 5 to page 20, line 27). Oligonucleotide hybridization is a well-established concept in molecular biology, dating back over 30 years; it is nothing if not routine.

Again, the nature of the invention, the state of the art and the predictability of the art are intertwined and support enablement. While biotechnological inventions are often considered unpredictable, this area of biotechnology is routinely practiced in the art. The use of

oligonucleotides to bind and screen for nucleic acids has been known in the art for years. Making an oligonucleotide as claimed has been known in the art for over 20 years. *See* specification, page 12, line 2.

The amount of experimentation necessary to make and use the claimed oligonucleotides would be routine, given the guidance in the claims, the state of the art and the high level of skill in the art. It would be of a very routine nature to synthesize oligonucleotides that have 20-30 consecutive base pairs of a disclosed sequence and then screen the oligonucleotides to see if they hybridize under the very specific conditions set forth in the claims. A laboratory technician, as well as a scientist with a doctorate degree, could easily and routinely perform such experiments.

The claims provide more than enough guidance themselves for practicing the claimed invention. They recite the length of the oligonucleotide, the sequence to which it must be complementary, and the conditions upon which it would hybridize.

In conclusion, claims 18-20, as well as claims 8-10, 13-15, 17, 47-53 and 55, are fully enabled under 35 U.S.C. § 112, first paragraph.

Conclusion

In view of the above amendments and remarks, it is respectfully requested that the application be reconsidered and that all pending claims be allowed and the case passed to issue. If there are any other issues remaining which the Examiner believes could be resolved through

either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

Dated: February 23, 2005

Respectfully submitted,

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